

REMARKS

Claims 1-21 and 29-50 are pending. Claims 34-50 are withdrawn as being directed to a non-elected invention. Claims 16 and 29-31 are rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claims 1, 7-10, 13, 17, and 19 are rejected under 35 U.S.C. § 102 for anticipation by WO 99/01034. Claims 1-15, 17, 19-21, 29, and 32 are rejected under 35 U.S.C. § 103(a) for obviousness over WO 99/01034 and WO 00/69449 in view of Keller et al. (Frontiers in Bioscience, 1996; hereinafter “Keller”), Hibberts et al. (Journal of Endocrinology, 1998; hereinafter “Hibberts”), and Van Nispen (U.S. Patent No. 5,002,881; hereinafter “Van Nispen”). Finally, claims 1, 18, and 33 are rejected under 35 U.S.C. § 103(a) for obviousness over WO 99/01034. By this reply, Applicants cancel claims 2-6, amend claims 1, 9, 16, 30, and 31, and address each of the Examiner’s rejections. Applicants reserve the right to pursue cancelled subject matter in a continuation application.

Support for the Amendment

Support for the amendment to claims 1 and 9 is found in prior claim 4. Claims 16, 30, and 31 are amended to clarify the claimed subject matter. No new matter is added by the amendment.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 16, 30, and 31, stating “[c]laims 16, 30, and 31 fail to distinctly claim applicant’s invention because ‘a serum-free component’ of the conditioned medium is claimed. It is unclear if this ‘component’ is separate from the medium” (Office

Action, p. 2). Applicants have amended claims 16, 30, and 31 to replace the term “component” with the term “constituent,” which more clearly indicates that the serum free constituent is an additive present in the conditioned medium and is not separate from the conditioned medium. This rejection can now be withdrawn.

The Examiner also rejects claim 29, stating “[i]t is unclear what an ‘established’ cell line is in regards to applicant’s invention” (Office Action, p. 2). Applicants respectfully traverse this rejection.

An established cell line, also known as an immortalized cell line, is well known in the art to refer to cells which have acquired the ability to proliferate indefinitely given appropriate medium and conditions. Cells in an established cell line are distinguished from primary cells, which are cultured directly from tissue and have not acquired the ability to proliferate indefinitely. Because the term “established,” when used to modify a the phrase “cell line,” is described in the specification (see, e.g., page 5, lines 14-24) and is well known to those skilled in the art, Applicants respectfully submit that the term established is not unclear and this rejection should be withdrawn.

Rejections under 35 U.S.C. § 102

The Examiner rejects claims 1, 7-10, 13, 17, and 19 under 35 U.S.C. § 102 for anticipation by WO 99/01034, stating that “WO 99/01034 discloses a method for producing new hair growth comprising culturing human dermal papilla cells in a medium conditioned with human keratinocytes” (Office Action, p. 3). Applicants have amended present claim 1 to recite that the culture medium is conditioned by prostate epithelial cells. WO 99/01034 only discloses

culturing human dermal papilla cells using a culture medium supplemented with a conditioned medium from a culture of *normal human keratinocytes*. WO 99/01034 fails to teach or suggest a method for cultivating hair inductive cells using a culture medium supplemented with a conditioned medium from *prostate epithelial cells*. For this reason, WO 99/01034 fails to teach or suggest all of the limitations of present claim 1, and claims dependent therefrom, as is required to establish an anticipation under 35 U.S.C. § 102 (see, e.g., M.P.E.P. § 2131). This rejection can now be withdrawn.

Rejections under 35 U.S.C. § 103(a)

WO 99/01034 and WO 00/69449 in view of Keller, Hibberts, and Van Nispen

Claims 1-15, 17, 19-21, 29, and 32 are rejected under 35 U.S.C. § 103(a) for obviousness over WO 99/01034 and WO 00/69449 in view of Keller, Hibberts, and Van Nispen. The Examiner states:

WO 99/01034 discloses a method for producing new hair growth comprising culturing human dermal papilla cells in a medium conditioned with human keratinocytes... WO 00/69449 disclose conditioned cell culture medium compositions and their methods of use. The medium may be conditioned with any eukaryotic cell type... including... [cells of the] **genitourinary tract**, i.e. encompassing the prostate (p. 12, lines 13-20)... *Neither reference teaches cultivating hair inductive cells such as dermal papilla or sheath cells in conditioned medium conditioned with prostate epithelial cells.* (Office Action, pp. 4-7; emphasis added.)

Thus, as is acknowledged by the Examiner, both WO 99/01034 and WO 00/69449 fail to teach or suggest all of the limitation of claims 1-15, 17, 19-21, 29, and 32, as presently amended, because they fail to teach or suggest the use of a medium conditioned by prostate epithelial cells for any reason, much less to cultivate hair inductive cells (Office Action, p. 7). Nonetheless, the

Examiner states:

WO 00/69449 strongly suggests a culture media used for cultivation of cells used in a method for stimulating hair growth, particularly they disclose a media conditioned with cells from the genitourinary tract, i.e., prostate epithelial cells, which is formulated to culture cells used in methods of stimulating hair growth. Given what is known in the art of the importance of dermal papilla cells in the development of hair, it would be obvious to one of ordinary skill in the art at the time of the invention to cultivate dermal papilla cells in a conditioned medium formulated for stimulating hair growth. (Office Action, p. 7.)

As is discussed in detail below, the Examiner has grossly mischaracterized the disclosure of WO 00/69449 to establish a *prima facie* case of obviousness against present claims 1-15, 17, 19-21, 29, and 32. Contrary to the Examiner's conclusion, the combination of WO 99/01034 and WO 00/69449, even in view of Keller, Hibberts, and Van Nispen, fails to establish a *prima facie case* of obviousness against present claims 1-15, 17, 19-21, 29, and 32 because none of these references, either alone or in combination, teaches or suggest a method for cultivating hair inductive cells using a culture medium supplemented with a conditioned medium from prostate epithelial cells.

*WO 99/01034 and WO 00/69449 Fail to Teach or Suggest
All of the Limitation of Present Claims 1-15, 17, 19-21, 29, and 32*

WO 99/01034 is discussed *supra*. WO 00/69499 merely discloses the use of various cell types for preparing conditioned cell media. WO 00/69499 further discloses that the conditioned media can be formulated for topical application to the skin to stimulate hair growth. WO 00/69499 clearly fails to teach or suggest using a conditioned medium prepared using prostate epithelial cells to supplement a culture medium that is used to cultivate hair inductive cells, as is recited in present claims 1-15, 17, 19-21, 29, and 32. The Examiner, though, in her attempt to

establish a *prima facie* case of obviousness, mischaracterizes WO 00/69499 to provide support for an unrelated proposition, which is that WO 00/69449 discloses the use of prostate epithelial cells to prepare a conditioned medium, which is then used to stimulate hair growth (Office Action, p. 6). Not only is this conclusion incorrect, it has nothing to do with the method of present claims 1-15, 17, 19-21, 29, and 32. WO 00/69499 merely discloses that medium conditioned by *human papilla cells* can be applied topically to the skin to stimulate hair growth (see p. 45-46). Applicants' invention, as recited in present claim 1, and claims dependent therefrom, is not the stimulation of hair growth, but rather a method for cultivating hair inductive cells by culturing the hair inductive cells in a culture medium supplemented with a medium conditioned by prostate epithelial cells. This is not taught or suggested by WO 00/69499.

In addition, WO 00/69449 fails to teach or suggest the use of prostate epithelial cells for any purpose. The portion of WO 00/69499 cited by the Examiner to support the proposition that prostate epithelial cells are used to prepare a conditioned medium merely discusses using various types of *stem cells*, which are prepared from various tissues including tissue of the genitourinary tract, to prepare three-dimensional tissue cultures for preparing conditioned cell media (see page 12, lines 13-20). Not once does WO 00/69449 mention prostate epithelial cells, nor is this cell type even suggested. Because WO 00/69449 only suggests that stem cells, and not prostate epithelial cells, can be obtained from tissue of the genitourinary tract for use in preparing conditioned cell media, WO 00/69499 clearly fails to teach or suggest this limitation of present claims 1-15, 17, 19-21, 29, and 32. Furthermore, WO 00/69499 simply fails to teach or suggest the *cultivation* of hair inductive cells, such as dermal papilla cells or dermal sheath cells, by culturing these cells in a medium conditioned by prostate epithelial cells. Thus, contrary to the

Examiner's conclusion, WO 00/69499 fails to "strongly suggest" a method for using a culture medium supplemented with a medium conditioned by prostate epithelial cells to cultivate hair inductive cells, as is required by present claims 1-15, 17, 19-21, 29, and 32.

WO 99/01034 and WO 00/69449, Alone or in Combination with Keller, Hibberts, and Van Nispen, Fail to Provide Any Motivation to Practice the Method of Present Claims 1-15, 17, 19-21, 29, and 32

After recognizing that neither WO 99/01034 nor WO 00/69449 teaches or suggests all the limitations of present claims 1-15, 17, 19-21, 29, and 32, the Examiner next makes a strained attempt to derive motivation to practice the method of present claims 1-15, 17, 19-21, 29, and 32 based on the knowledge of one skilled in the art, as demonstrated by Keller, Hibberts, and Van Nispen. The Examiner states:

It is known in the art that the development of the hair follicle depends on a mesenchymal-epithelial interaction, i.e., dermal papilla-keratinocytes. The same is true for prostate tissue, i.e. prostate stroma-prostate epithelial cells, as is disclosed by Keller...It is also known that androgen plays a role in the development of both. (Office Action, pp. 7-8.)

Hibberts...disclose that androgens are the most obvious regulators of normal hair growth and are a prerequisite for male pattern baldness. As is known in the art, the hair follicle is composed mainly of epithelial cells which protrudes down to the epidermis and dermis of the skin, enveloping at the base the mesenchyme-derived dermal papilla cells. Androgens act on the hair follicle via the mesencyme-derived [sic] dermal papilla, altering the production of mitogenic factors and extracellular matrix factors, which influence the epithelial cells. (Office Action, p. 8.)

Based on Keller and Hibberts, the Examiner concludes:

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have cultivated hair inductive cells such as dermal papilla cells in a medium conditioned with prostate epithelial cells because it is known in the art that both hair follicles and the prostate develop via mesenchymal-epithelial

interactions, i.e dermal papilla-keratinocytes and prostate stroma-prostate epithelial cells and both hair follicle and prostate development are androgen modulated, plus there has been an observed association between men with male pattern baldness and benign prostate hyperplasia..., **therefore, one would expect to establish the required mesenchymal-epithelial interaction between dermal papilla cells and prostate epithelial cells required for hair follicle development.** (Office Action, pp. 8-9; emphasis added.)

Applicants note that Van Nispen is cited simply for its disclosure of ultrafiltration, which is an element of present claim 32 (Office Action, p. 9).

The Examiner's conclusion of sufficient "motivation" and "expectation of success" based on the combination of Keller, Hibberts, and Van Nispen with WO 99/01034 and WO 00/69499 is misguided. Like WO 99/01034 and WO 00/69449, none of Keller, Hibberts, or Van Nispen provides any teaching or suggestion to cultivate hair inductive cells by culturing these cells in a culture medium supplemented with a medium conditioned by prostate epithelial cells. Absent this teaching or suggestion, there can be no motivation to combine the cited references, and thus, a *prima facie* case of obviousness under 35 U.S.C. § 103 has not been established.

In the present case, the Examiner has merely identified various elements of the present claims in the cited art. These elements have been combined without a specific suggestion or motivation for such a combination found in the disclosures of any of the cited references. The Examiner has failed to demonstrate that the cited references teach, suggest, or motivate the skilled artisan to combine their reference teachings, much less that this combination of references even yields the invention of present claims 1-15, 17, 19-21, 29, and 32.

For example, the Examiner, relying solely on Keller, Hibberts, and Van Nispen, concludes:

It would have been obvious to one skilled in the art...to have cultivated hair inductive cells such as dermal papilla cells in a medium conditioned with prostate

epithelial cells because it is known in the art that both hair follicles and the prostate develop via mesenchymal-epithelial interactions, i.e., dermal papilla-keratinocytes and prostate stroma-prostate epithelial cells and both hair follicle and prostate development are androgen modulated, plus there has been an observed association between men with male pattern baldness and benign prostate hyperplasia...therefore, one would expect to establish the required mesenchymal-epithelial interaction between dermal papilla cells and prostate epithelial cells required for hair follicle development. (Office Action, pp. 8-9.)

Thus, the Examiner suggests that Keller, Hibberts, and Van Nispen provide a connection in the art between dermal papilla and prostate epithelial cells and thus, when combined with WO 99/01034 and WO 00/69449, this combination would lead the skilled artisan to the method of present claims 1-15, 17, 19-21, 29, and 32. This conclusion is in error.

Keller merely discusses, *inter alia* and in very general terms, the effect of androgens on the growth of hair follicles by modulating the action of dermal papilla cells (see p. 62 of Keller). Keller also discloses that androgens modulate the expression of growth factors in prostate epithelial cells (see p. 63 of Keller). Keller fails to teach or suggest any interaction between dermal papilla cells and prostate epithelial cells, much less that one skilled in the art should cultivate dermal papilla cells in a culture medium supplemented with a medium conditioned by prostate epithelial cells. Likewise, Hibberts, which merely discloses that dermal papilla cells derived from balding scalp hair follicles express greater levels of high affinity androgen receptors (see the abstract and p. 64 of Hibberts), fails to teach or suggest the cultivation of dermal papilla cells in a culture medium supplemented with a medium conditioned by prostate epithelial cells. Finally, Van Nispen simply discloses a method for preparing lactic acid by a method that involves, *inter alia*, ultrafiltration of a reaction mixture fermented by bacilli (see, e.g., the abstract). Van Nispen also fails to teach or suggest the method of present claim 1, and claims

dependent therefrom.

Clearly, Keller, Hibberts, and Van Nispen lack any teaching or suggestion of the method of present claim 1. Accordingly, their combination fails to cure the deficiencies of WO 99/01034 and WO 00/69449. Even if this combination of references did disclose all of the limitations of present claim 1, and claims dependent therefrom, which they do not, the skilled artisan would not be motivated to combine their reference teachings to arrive at the method of present claims 1-15, 17, 19-21, 29, and 32 because these references lack an objective reason for making the combination (“the mere fact that these references can be combined or modified does not render the resultant combination obvious unless the prior art references also suggest the desirability of the combination,” M.P.E.P. § 2143.01(III) (citation omitted; emphasis in original)). Thus, in addition to the fact that these references fail to teach or suggest all of the limitations of present claims 1-15, 17, 19-21, 29, and 32, there is simply no motivation to combine WO 99/01034 and WO 00/69449 with Keller, Hibberts, and Van Nispen due to the lack of any teaching or suggestion in the references themselves of the desirability of the combination. For this reason as well, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, the rejection of claims 1-15, 17, 19-21, 29, and 32 should be withdrawn.

*The Suggestion to Combine the Cited References and the
Expectation of Success is Found Solely in Appellants’ Disclosure*

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the prior art must not only suggest the claimed combination, but must also provide a reasonable expectation of success; these elements cannot be derived solely from Applicants’ disclosure (see *In re Vaeck*,

947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991), and *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988)). As is discussed above, WO 99/01034 and WO 00/69449 fail to teach or suggest the cultivation of dermal papilla cells in a culture medium supplemented with a medium conditioned by prostate epithelial cells, and Keller, Hibberts, and Van Nispen fail to provide any teaching, suggestion, or motivation that cures this deficiency. The Examiner has not established a clear motivation provided solely from the cited references that would guide the skilled artisan to combine the reference teachings to yield the invention recited in claims 1-15, 17, 19-21, 29, and 32 prior to the disclosure of Applicants' present invention, nor any expectation of success other than that derived from the teachings of Applicants' disclosure. Therefore, both the motivation to combine the cited references and the reasonable expectation of success have been derived solely from the teachings of Applicants' disclosure.

The use of Applicants' disclosure to provide a motivation for combining the cited references and to derive a reasonable expectation of success is an improper use of hindsight and cannot form the basis of an obviousness rejection. The Federal Circuit has repeatedly cautioned against the "insidious effects of hindsight" in making obviousness determinations. *Life Technologies, Inc. v. Clontech Labs, Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000). More specifically, the court has stated:

it is impermissible to first ascertain factually what [Applicants] did and then view the prior art in such a manner as to select from the random facts of art only those which may be modified and then utilized to reconstruct appellants invention from such prior art. (*Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985).)

To avoid the use of hindsight, the M.P.E.P. has adopted the same view, stating that "the mere

fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness," and that the art must provide "an *objective* reason to combine the teachings." M.P.E.P. § 2143.01; emphasis added. Further, a generally high level of skill in the art cannot be relied upon to provide such a reason. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999). Thus, absent a specific motivation to combine references, a *prima facie* case of obviousness cannot be made.

Because the prior art does not teach, suggest, or motivate the skilled artisan to cultivate hair inductive cells in a culture medium supplemented with a medium conditioned by prostate epithelial cells, as is recited in present claims 1-15, 17, 19-21, 29, and 32, and because the cited references fail to provide a reasonable expectation of success that a culture medium supplemented with a medium conditioned by prostate epithelial cells would promote the growth of hair inductive cells while maintaining their hair inductive potential, absent the guidance provided by Applicants' disclosure, Applicants respectfully submit that the Examiner has relied upon improper hindsight to form the basis for the rejection of claims 1-15, 17, 19-21, 29, and 32 for obviousness. Therefore, Applicants respectfully request that, for this reason as well, the rejection of claims 1-15, 17, 19-21, 29, and 32 under 35 U.S.C. § 103(a) over the combination of WO 99/01034 and WO 00/69499 in view of Keller, Hibberts, and Van Nispen should be withdrawn.

WO 99/01034

Claims 1, 18, and 33 are rejected under 35 U.S.C. § 103(a) for obviousness over WO 99/01034. The Examiner states:

WO 99/01034 discloses a method for producing new hair growth comprising culturing human dermal papilla cells in a medium conditioned with human keratinocytes...Although WO'034 does not specifically teach the number of passages of the dermal papilla cells, they do teach that the cells can expand for many passages and further teach the ability of rat cells under the same conditions to retain their hair inducing properties through 56 passages...Thus, it would be obvious to one or ordinary skill in the art at the time the invention was made to cultivate dermal papilla cells in a conditioned medium with cells of non-epidermal origin and expect success in maintaining hair inducing properties through passages of more than seven." (Office Action, pp. 9-12.)

As is discussed above, Applicants have amended present independent claim 1 to recite a method for cultivating hair inductive cells using a culture medium supplemented with a medium conditioned by prostate epithelial cells. This limitation is not taught or suggested by WO 99/01034. For this reason, WO 99/01034 fails to teach or suggest all of the limitations of present claim 1, and claims dependent therefrom, as is required to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a) (see, e.g., M.P.E.P. § 2142). This rejection can now be withdrawn.

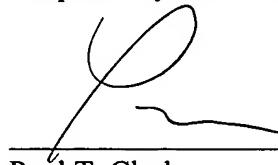
CONCLUSION

In view of the above remarks, Applicants respectfully submit that the present claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for two months, to and including January 22, 2007, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any additional charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,



Paul T. Clark
Reg. No. 30,162

Date: Jan. 22, 2007
Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045